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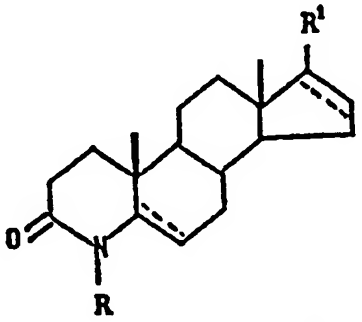
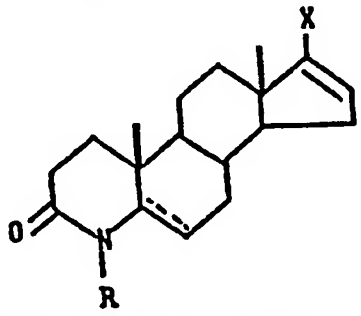
(54) Title: NOVEL PROCESS FOR PREPARING 17β-SUBSTITUTED 4-AZAANDROSTANE DERIVATIVES

(57) Abstract

The invention relates to a novel process for preparing 17β-substituted 4-azaandrostane derivatives of general formula (I) wherein R represents hydrogen or a C_{1-3}alkyl group; R^1 represents a carboxamido group mono- or disubstituted by C_{1-5}alkyl group(s); or a free carboxyl group; or a carboxyl group esterified with a C_{1-5} alcohol; and the —— bond line represents a single or double bond; as well as their salts. The process comprises reacting a 17-halogeno-4-azaandrostene derivative of general formula (II) wherein R and the —— bond line are as defined above, and X is chlorine, bromine or iodine, with a primary or secondary alkylamine or a C_{1-5} alcohol, in dimethylformamide or dimethylsulfoxide medium in the presence of a palladium(II) salt and phosphines or a palladium(II) complex and a tertiary amine base in carbon monoxide atmosphere at a temperature between 35 °C and 80 °C, then, if desired, transforming an obtained compound of general formula (I) to another compound of general formula (I) by hydrogenation, hydrolysis or salt forming reaction.



(I)



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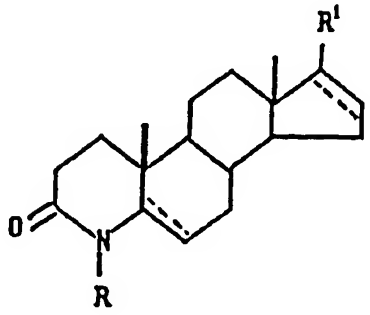
NOVEL PROCESS FOR PREPARING 17ß-SUBSTITUTED 4-AZAANDROSTANE DERIVATIVES

This invention relates to a novel process for preparing 17ß-substituted 4-azaandrostane derivatives of general formula (I)



(I)

wherein

R represents hydrogen or a C_{1-3}alkyl group;

R^1 represents a carboxamido group mono- or disubstituted by straight or branched chain C_{1-8}alkyl group(s); or a free carboxyl group; or a carboxyl group esterified with a straight or branched chain C_{1-5} alcohol; and the

---- bond line represents a single or double bond;

as well as their salts formed with pharmaceutically acceptable bases when R^1 is a free carboxyl group.

The compounds of general formula (I) inhibit the 5α-reductase enzyme and therefore, they block the transformation of testosterone to dihydrotestosterone. Thus, the compounds of general formula (I) are useful for the healing of dihydrotestosterone-dependent diseases, e.g. prostatic hyperplasia, acne vulgaris, seborrhoea or female hirsutism.

According to literature references [European patent

No. 4,949; as well as J. Med. Chem. 27, pages 1690 to 1701 (1984)] the preparation of the known compounds of general formula (I) can be accomplished in the manner described hereinafter.

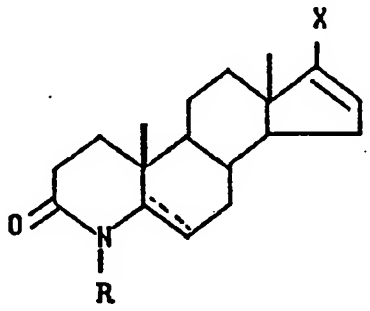
After reacting pregnenolone (3ß-hydroxy-5-pregnen--20-one) with elemental iodine in pyridine, then the "21-pyridinium iodide" obtained is cleaved at the bond between C_{20} and C_{21} by using sodium methoxide to obtain the corresponding "17-carbomethoxy derivative". The obtained 3ß-hydroxy-17ß-carbomethoxyandrost-5-ene is oxidized by aluminum isopropoxide in the presence of cyclohexanone in toluene, subsequently the carbomethoxy group is hydrolyzed to the carboxylic acid and transformed to the "17-carboxylic acid chloride" by using oxalyl chloride. This acyl chloride is converted to e.g. "17ß-(N,N-diethylcarbamoyl)" derivative by using diethylamine. After oxidizing the thus obtained 17ß-(N,N-diethylcarbamoyl)androst-4-en-3-one to "seco acid" by using sodium periodate in tertiary butanol in the presence of potassium permanganate, the seco compound is reacted with ammonia or an other primary amine in ethylene glycol to obtain e.g. 3-oxo-4-methyl-4-aza-androst-5-ene-17ß-(N,N-diethylcarboxamide). This latter substance is hydrogenated to the corresponding "4-aza--5α-androstane" derivative in glacial acetic acid in the presence of hydrogen and platinum oxide catalyst. After isolation the final products are purified in various ways.

The starting substance of the process described in the literature is pregnenolone, which is obtained by hydrogenating the double bond in position 16 of pregnadienolone acetate obtained by the decomposition of diosgenin or solasodin of natural origin. However, the availability of pregnenolone is decreasing because the Dioscorea species growing wild in Mexico is on the

verge of dying off. The root of this plant is used for extracting diosgenin. On the other hand, the cultivation of Solanum aviculare and the isolation of solasodin therefrom are not economical according to our experience.

Considering their therapeutic activity, there exists a continuous demand on the target compounds in the pharmaceutical industry, however, this demand is more and more difficult to satisfy by using the known process of preparation because those discussed above.

The aim of the present invention is to develop a preparation process from a starting material which is easily available. From this point of view the new 17--halogeno-4-azaandrostene derivatives of general formula (II)



(II)

proved to be suitable.

Surprisingly, it has been found that a process completely satisfying the above demands for preparing the target compounds of general formula (I) can be accomplished by

reacting a 17-halogeno-4-azaandrostene derivative of general formula (II), wherein R and the ---- bond line are as defined above, and X is chlorine, bromine or iodine, with a primary or secondary alkylamine containing a C_{1-8}alkyl group or a straight or branched chain C_{1-5} alcohol, respectively in dimethylformamide

or dimethylsulfoxide medium in the presence of a palladium(II) salt and phosphines or a palladium(II) complex and a tertiary amine base in carbon monoxide atmosphere at a temperature between 35 °C and 80 °C,

then, if desired, hydrogenating a compound of general formula (I) containing a double bond as ---- bond line in the presence of a catalyst to obtain a compound of general formula (I) containing a single bond as ---- bond line, and/or

hydrolyzing in a known way a thus obtained compound of general formula (I) containing an esterified carboxyl group as R^1 to obtain a compound of general formula (I) containing a free carboxyl group as R^1, and/or

transforming a thus obtained compound of general formula (I) containing a free carboxyl group as R^1 to its salt by reacting it with a pharmaceutically acceptable base.

According to a preferred embodiment of the invention a compound of general formula (II) is reacted with a primary or secondary amine in dimethylformamide in the presence of palladium(II) acetate, triphenylphosphine and triethylamine under carbon monoxide at 60 °C for 90 to 120 minutes. After the reaction has become complete, the amines and dimethylformamide are distilled off under reduced pressure, the residue is dissolved in chloroform and successively washed with water, aqueous hydrochloric acid solution, aqueous sodium hydrogen carbonate solution and again with water until neutral. After drying and evaporating the solvent, the residue is purified by chromatography or recrystallization or by using both methods.

If desired, the double bond [being in position 16 or in positions 5 and 16 depending on the starting compound of general formula (II)] of the obtained

compounds of general formula (I) containing a mono- or disubstituted carboxamido group as R^1 may be hydrogenated in the presence of gaseous hydrogen and charcoal supported palladium catalyst in formic acid or in the presence of hydrogen and platinum oxide catalyst in glacial acetic acid.

For preparing compounds of general formula (I) containing an alkoxycarbonyl group as R^1, a compound of general formula (II) is preferably reacted with a C_{1-5} alkanol in dimethylsulfoxide, in the presence of a mixture of palladium(II) acetate, 1,4-bis(diphenylphosphino)butane and triethylamine under carbon monoxide at 60 °C for 10 to 15 hours. After the reaction has become complete, the volatile components are distilled off under reduced pressure, the residue is dissolved in chloroform and the water-soluble components are removed by washing with water. After drying the solution and evaporating the solvent, the residue is purified by chromatography or recrystallization or by using both methods.

If desired, the obtained compound of general formula (I) is hydrogenated as described above, i.e. in formic acid in the presence of hydrogen and charcoal supported palladium or in glacial acetic acid in the presence of hydrogen and platinum oxide as catalyst and/or optionally hydrolyzed to the corresponding 17β--carboxylic acid derivative in alkaline medium.

In the process according to the invention 1,4-bis(diphenylphosphino)butane, 1,2-bis(diphenylphosphino)ethane, triphenylphosphine or 1,3-bis(diphenylphosphino)propane is preferably used as a phosphine although a complex of the above phosphines with palladium(II) salts may also be employed: e.g. the reaction is carried out at 35 to 60 °C with primary or secondary amines and at 40 to 80 °C with C_{1-5} alcohols

in the presence of bis(triphenylphosphino)palladium(II) dichloride.

The process according to the invention provides the use of the easily available 3-keto-Δ^4 derivatives as starting substances, which can be obtained by the decomposition of sitosterin. According to the invention the building-up of the 17-carboxamido or 17-carboalkoxy group, respectively can safely be carried out and the scale increase of the process needed for the industrial utilization is not burdened by any problem.

The starting substances used in the process according to the invention such as "4-aza-17-hydrazone" derivatives as well as the compounds of general formula (II) are new. Similarly, the unsaturated 4-aza-17-carboxamido- as well as 4-aza-17-alkoxycarbonyl derivatives of general formula (I) are also novel compounds. The saturated 4-aza-17-carboxamido derivatives as well as the saturated 4-aza-17-methoxycarbonyl derivative are known from the literature [European patent No. 4,949; J. Med. Chem. 27, pages 1690 to 1701 (1984)].

The novel 17-halogeno-4-azaandrostene derivatives of general formula (II) used as starting substances in the process of the present invention can be prepared as follows.

4-Aza-5α-androstane-3,17-dione, 4-methyl-4-aza-androstane-3,17-dione as well as 4-azaandrost-5-ene--3,17-dione (hereinafter named as 4-aza-17-keto derivatives), which are known compounds, can be prepared by a process described in the literature [J. Pharm. Sci. 63, pages 19 to 23 (1974); J. Med. Chem. 27, pages 1690 to 1701 (1984); J. Org. Chem. 46, pages 1442 to 1446 (1981)] from the known 17ß-hydroxy-androst-4-en-3-one.

The known "4-aza-17-keto derivatives" are reacted with hydrazine hydrate in ethanol in the presence of

triethylamine, after working up the reaction mixture (carried out as described in Example 1) the "hydrazone derivatives" formed are isolated and the crude products are immediately used without any purification for preparing the 17-halogeno-4-azaandrostene derivatives of general formula (II) as described hereinafter.

For the preparation of 17-iodo-4-azaandrostene derivatives the "hydrazone derivatives" are dissolved in chloroform or benzene or in a mixture thereof or in tetrahydrofuran and then reacted with elemental iodine in the presence of a tertiary amine base at room temperature. After complete reaction the compounds of general formula (II) are obtained as described in Example 4.

For the preparation of 17-halogeno-4-azaandrostene derivatives containing chlorine or bromine in position 17, the "hydrazone derivatives" are dissolved in pyridine optionally substituted by C_{1-4}alkyl group and reacted with N-chloro or N-bromosuccinimide, respectively at a temperature between -10 °C and +10 °C. The resulted compound of general formula (II) is isolated as described in Example 7.

The process according to the invention is illustrated in detail by the following non-limiting Examples.

Example 1

Preparation of 17-hydrazono-4-aza-5α-androstan-3-one

To a suspension containing 10 g (0.0346 mol) of 4-aza-5α-androstane-3,17-dione in 100 ml of ethanol 14 ml (0.1 mol) of triethylamine and 50 ml (1.0 mol) of hydrazine hydrate are added and the mixture is boiled under reflux for 3 hours. (The progress of the reaction is followed by thin layer chromatography.) After the

reaction has become complete the reaction mixture is cooled down, the solution is evaporated to one tenth of its original volume and the product is precipitated by adding about a 10-fold volume of water. After compaction the precipitate is filtered, washed with water until neutral and dried to obtain the title compound.
Yield: 9.44 g (90%), m.p.: 254-258 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.86 (s,3H,18-CH_3), 0.93 (s,3H,19-CH_3), 2.41 (m,2H,H-2), 3.07 (dd,1H,H-5), 4.77 (br,2H,NH_2), 5.74 (br,1H,NH).

Example 2
Preparation of 17-hydrazono-4-azaandrost-5-en-3-one

The process described in Example 1 is followed, except that 4-azaandrost-5-ene-3,17-dione is used as starting substance to obtain the title compound.
Yield: 35%, m.p.: 379-382 °C.
IR (KBr) ν: 1633 (C=C), 1661 (C=N), 1693 (C=O), 3200 (NH), 3350 (NH_2) cm^{-1}.

Example 3
Preparation of 17-hydrazono-4-methyl-4-aza-5α-androstan-3-one

The process described in Example 1 is followed, except that 4-methyl-4-aza-5α-androstane-3,17-dione is used as starting substance to give the title compound.
Yield: 75%, m.p.: 211-218 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.86 (s,3H,18-CH_3), 0.91 (s,3H,19-CH_3), 2.93 (s,3H,N-CH_3), 3.05 [dd(J=3.6; J=12.6), 1H, H-5], 4.78 (v br, 2H,NH_2).

Example 4

Preparation of 17-iodo-4-aza-5α-androst-16-en-3-one

After dissolving 9.1 g (0.03 mol) of 17-hydrazono-4--aza-5α-androstan-3-one in 1200 ml of an 1:1 chloroform/benzene mixture and adding 90 ml of triethylamine, 11.4 g (0.045 mol) of iodine dissolved in 110 ml of benzene are dropwise added to the above solution. The reaction mixture is stirred at room temperature for additional 60-90 minutes. (The progress of the reaction is followed by thin layer chromatography). After complete occurrence of the reaction the obtained solution is diluted with 500 ml of chloroform and successively washed with 10% aqueous hydrochloric acid solution, water, 5% aqueous sodium thiosulfate solution, water, 5% aqueous sodium hydrogen carbonate solution, finally with water and dried over anhydrous sodium sulfate. After evaporating the solvents under reduced pressure the residue is purified by chromatography on a silica gel column by using first chloroform and subsequently a 95:5 chloroform/acetone mixture as eluents. The product obtained is recrystallized from ethanol to give the title compound. Yield: 5.9 g (50%), m.p.: 278-282 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.73 (s,3H,18-CH_3), 0.91 (s,3H,19-CH_3), 3.1 (dd,1H,H-5), 6.18 (m,1H,H-16), 6.9 (br, 1H, NH).

Example 5

Preparation of 17-iodo-4-azaandrosta-5,16-dien-3-one

The process described in Example 4 is followed, except that 17-hydrazono-4-azaandrost-5-en-3-one is used as starting substance to obtain the title compound. Yield: 57%, m.p.: 227-230 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.78 (s,3H,18-CH_3), 1.13 (s,3H,19-CH_3), 4.9 [dd(J=2.4; J=5.1),1H,H-6], 6.15 [dd(J=3.2; J=1.7),1H,H-16], 8.27 (br,1H,NH).

Example 6

Preparation of 17-iodo-4-methyl-4-aza-5α-androst-16-en--3-one

The process described in Example 4 is followed, except that 17-hydrazono-4-methyl-4-aza-5α-androstan-3-one is used as starting substance and the reaction is carried out in benzene. The title compound is obtained in a yield of 52%, m.p.: 176-181 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.74 (s,3H,18-CH_3), 0.92 (s,3H,19-CH_3), 2.94 (s,3H,N-CH_3), 3.07 [dd(J=3.7; J=12.6), 1H, H-5], 6.13 [dd(J=3.2; J=1.7),1H,H-16].

Example 7

Preparation of 17-chloro-4-methyl-4-aza-5α-androst--16-en-3-one

A solution containing 4 g (0.0126 mol) of 17--hydrazono-4-methyl-4-aza-5α-androstan-3-one in 40 ml of anhydrous pyridine is cooled to 0 °C and the solution of 3.2 g (0.024 mol) of N-chlorosuccinimide in 40 ml of pyridine is dropwise added under vigorous stirring. After cessation of the violent nitrogen gas evolution the reaction mixture is stirred for additional 15 minutes and then dropped to 800 ml of water. After compaction of the precipitate the crude product is filtered, washed with water until neutral and dried over phosphorus pentoxide under reduced pressure at room temperature. The crude product obtained is purified by chromatography on a silica gel

column by using chloroform as eluent. After recrystallization of the evaporation residue from petroleum ether the title compound is obtained in a yield of 2.15 g (53%), m.p.: 139-140 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.88 (s,3H,18-CH_3), 0.93 (s,3H,19-CH_3), 2.89 (s,3H,N-CH_3), 3.0 (dd,1H,H-5), 5.53 (m,1H,H-16).

Example 8

Preparation of 17-bromo-4-methyl-4-aza-5α-androst-16--en-3-one

The process described in Example 7 is followed by using 17-hydrazono-4-methyl-4-aza-5α-androstan-3-one as starting substance and N-bromosuccinimide as reactant to give the title compound. Yield: 55%, m.p.: 159-161 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.82 (s,3H,18-CH_3), 0.91 (s,3H,19-CH_3), 2.86 (s,3H,N-CH_3), 3.0 (dd,1H,H-5), 5.68 (m,1H,H-16).

Example 9

Preparation of 3-oxo-4-aza-5α-androst-16-ene-17ß-(N--tert-butylcarboxamide)

To a solution containing 3.99 g (0.01 mol) of 17--iodo-4-aza-5α-androst-16-en-3-one in 150 ml of dimethylformamide, 0.224 g (0.001 mol) of palladium(II) acetate, 0.524 g (0.002 mol) of triphenylphosphine, 10 ml of triethylamine and 15 ml (0.14 mol) of tert-butylamine are added and the mixture is heated at 60 °C under carbon monoxide for 90 to 120 minutes. (The progress of the reaction is followed by thin layer and gas chromatography.) After the reaction has become complete the amines and dimethylformamide are distilled

off under reduced pressure, then the residue is dissolved in 150 ml of chloroform and successively washed with water, 5% aqueous hydrochloric acid solution, saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution until neutral and finally dried over anhydrous sodium sulfate. After evaporating the solvent the residue is purified by chromatography on a silica gel column by using ethyl acetate as eluent to obtain the title compound. Yield: 3.16 g (85%), m.p.: 292-297 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.93 (s,3H,19-CH_3), 1.0 (s,3H,18-CH_3), 1.4 (s,3H,$C(CH_3)_3$), 2.15 (m,2H,H-15a+H-15b), 2.4 (m,2H,H-2), 3.08 [dd (J=4.5; J=7.0),1H,H-5], 5.48 (br s,1H,NH), 5.6 (br s,1H,NH), 6.18 [dd (J=1.7; J=1.4),1H,H-16].

Example 10
Preparation of 3-oxo-4-aza-5α-androst-16-ene-17ß-[N--(2,2-dimethylpropyl)carboxamide]

The process described in Example 9 is followed by using 17-iodo-4-aza-5α-androst-16-en-3-one as starting substance and 2,2-dimethylpropylamine (neopentylamine) as reactant to obtain the title compound. Yield: 82%.
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.92 (s,9H,$C(CH_3)_3$), 0.95 (s,3H,19-CH_3), 1.02 (s,3H,18-CH_3), 2.4 (m,2H,H-2), 3.1 (m,3H, NCH_2, H-5), 5.66 (br s,1H,NH), 5.85 (br s,1H,NH), 6.3 (br s,1H, H-16).

Example 11
Preparation of 4-methyl-3-oxo-4-aza-5α-androst-16-ene--17-carboxylic acid methyl ester

A mixture containing 0.41 g (0.001 mol) of 17-iodo--4-methyl-4-aza-5α-androst-16-en-3-one, 0.0224 g

(0.1 mmol) of palladium(II) acetate, 0.0213 g (0.05 mmol) of 1,4-bis(diphenylphosphino)butane, 0.3 ml of triethylamine, 2 ml of methanol and 15 ml of dimethylsulfoxide is stirred under carbon monoxide at 60 °C for 10 to 15 hours. (The progress of the reaction is followed by thin layer and gas chromatography.) After complete reaction the mixture is evaporated under reduced pressure, the residue is dissolved in 15 ml of chloroform, the chloroform solution is washed 4 times with water and dried over anhydrous sodium sulfate. After evaporation of the solvent the residue is purified by chromatography on a silica gel column by using an 1:10 mixture of ethyl acetate/petroleum ether as eluent. The title compound is obtained in a yield of 0.014 g (40%), m.p.: 182-186 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.93 (s,6H,18-CH_3 + + 19-CH_3), 2.45 (m,2H,H-2), 2.94 (s,3H,NCH_3), 3.07 (dd,1H,H-5), 3.72 (s,3H,OCH_3), 6.76 (br s,1H,H-16).

Example 12

Preparation of 3-oxo-4-aza-5α-androst-16-ene-17-carboxylic acid methyl ester

The process described in Example 11 is followed by using 17-iodo-4-aza-5α-androst-16-en-3-one as starting substance to give the title compound. Yield: 42%, m.p.: 270 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.92 (s,3H,19-CH_3), 0.94 (s,3H,18-CH_3), 2.4 (m,2H,H-2), 3.07 (dd,1H,H-5), 3.72 (s,3H,OCH_3), 6.15 (br s,1H,NH), 6.75 (br s,1H,H-16).

Example 13

Preparation of 3-oxo-4-azaandrosta-5,16-diene-17ß-(N--tert-butylcarboxamide)

The process described in Example 9 is followed by using 17-iodo-4-azaandrosta-5,16-dien-3-one as starting substance and tert-butylamine as reactant to give the title compound. Yield: 78%, m.p.: 266-269 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 1.04 (s,3H,18-CH_3), 1.14 (s,3H,19-CH_3), 1.38 (s,9H,$C(CH_3)_3$), 2.5 (m,2H,H-2), 4.88 [dd (J=2.1; J=2.7), 1H,H-6], 5.5 (br s,1H,NH), 6.2 [dd (J=1.8; J=0.9),1H,H-16], 8.08 (br s,1H,NH).

Example 14

Preparation of 4-methyl-3-oxo-4-aza-5α-androst-16-ene--17ß-(N,N-diethylcarboxamide)

a.)

The process described in Example 9 is followed by using 17-iodo-4-methyl-4-aza-5α-androst-16-en-3-one as starting substance and diethylamine as reactant. In this way the title compound is obtained in a yield of 84%, m.p.: 205-210 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 0.93 (s,3H,19-CH_3), 1.09 (s,3H,18-CH_3), 1.13 (t,6H,$N(CH_2CH_3)_2$), 2.94 (s,3H,NCH_3), 3.06 (dd,1H,H-5), 5.26 (m,1H,H-16).

b.)

The process described in Example 9 is followed by using 17-bromo-4-methyl-4-aza-5α-androst-16-en-3-one as starting substance and diethylamine as reactant. In this way the title compound is obtained in a yield of 85%, m.p.: 205-210 °C.

Example 15

Preparation of 4-methyl-3-oxo-4-aza-5α-androstane-17ß--(N,N-diethylcarboxamide)

A suspension containing 1 g of charcoal supported palladium catalyst in 6 ml of water is added to the solution of 1 g (2.6 mmol) of 4-methyl-3-oxo-4-aza-5α--androst-16-ene-17ß-(N,N-diethylcarboxamide) in 40 ml of formic acid under nitrogen. The heterogeneous mixture is stirred at room temperature for 4 to 5 hours while observing the progress of the reduction by thin layer chromatography. After the reaction has become complete the catalyst is filtered off and washed with an 1:1 mixture of chloroform/methanol. After evaporating the combined solution to dryness the evaporation residue is thoroughly triturated with water, the precipitate is filtered and washed with water to obtain the title compound. Yield: 0.88 g (87%), m.p.: 180-181 °C (after recrystallyzation from ethyl acetate).

Example 16

Preparation of 3-oxo-4-aza-5α-androstane-17ß-(N-tert--butylcarboxamide)

The process described in Example 15 is followed by using 3-oxo-4-aza-5α-androst-16-ene-17ß-(N-tert-butylcarboxamide) as starting substance to obtain the title compound. Yield: 90%, m.p.: 283-286 °C.

Example 17

Preparation of 3-oxo-4-aza-5α-androstane-17β-carboxylic acid methyl ester

The process described in Example 15 is followed by using 3-oxo-4-aza-5-androst-16-ene-17-carboxylic acid methyl ester as starting substance to give the title compound. Yield: 85%, m.p.: 301-304 °C (after re-crystallization from ethyl acetate).

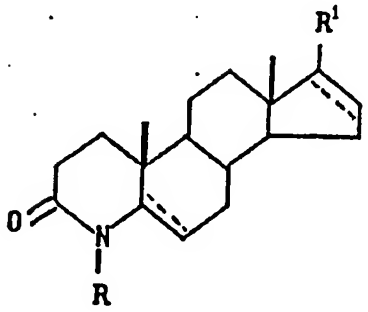
Example 18

Preparation of 3-oxo-4-aza-5α-androstane-17β-(N-tert--butylcarboxamide)

The process described in Example 15 is followed by using 3-oxo-4-azaandrosta-5,16-ene-17β-(N-tert-butyl-carboxamide) as starting substance to obtain the title compound. Yield: 70%, m.p.: 283-286 °C.

Claims

1. A process for the preparation of 17ß-substituted 4-azaandrostane derivatives of the general formula (I),



(I)

wherein

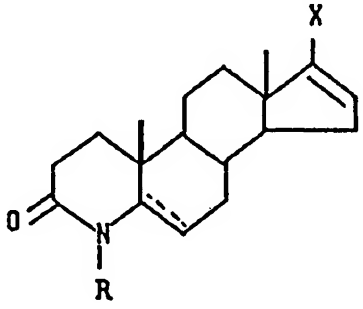
R represents hydrogen or a C_{1-3}alkyl group;

R^1 represents a carboxamido group mono- or disubstituted by straight or branched chain C_{1-8}alkyl group(s); or a free carboxyl group; or a carboxyl group esterified with a straight or branched chain C_{1-5} alcohol; and the

---- bond line represents a single or double bond;

as well as their salts formed with pharmaceutically acceptable bases when R^1 is a free carboxyl group, **which c o m p r i s e s,**

reacting a 17-halogeno-4-azaandrostene derivative of general formula (II),



(II)

wherein R and the ---- bond line are as defined above, and X is chlorine, bromine or iodine, with a primary or secondary alkylamine containing a C_{1-8}alkyl group or a straight or branched chain C_{1-5} alcohol, respectively in dimethylformamide or dimethylsulfoxide medium in the presence of a palladium(II) salt and phosphines or a palladium(II) complex and a tertiary amine base in carbon monoxide atmosphere at a temperature between 35 °C and 80 °C,

then, if desired, hydrogenating an obtained compound of general formula (I) containing a double bond as ---- bond line, wherein R and R^1 are as defined for the general formula (I), in the presence of a catalyst to obtain a compound of general formula (I) containing a single bond as ---- bond line, wherein R and R^1 are as defined for the general formula (I), and/or

hydrolyzing in a known way a thus obtained compound of general formula (I) containing an esterified carboxyl group as R^1, wherein R and the ---- bond line are as defined for the general formula (I), to obtain a compound of general formula (I) containing a free carboxyl group as R^1, wherein R and the ---- bond line are as defined for the general formula (I), and/or

transforming a thus obtained compound of general formula (I), wherein R and the ---- bond line are as defined for the general formula (I) and R^1 is a free carboxyl group, to its salt by reacting it with a pharmaceutically acceptable base.

2. A process as claimed in claim 1, **which c o m p r i s e s** using triethylamine as a tertiary amine base.

3. A process as claimed in claim 1 or claim 2, **which c o m p r i s e s,** using palladium(II) acetate or palladium(II) chloride as palladium(II)

salt.

4. A process as claimed in any of the claims 1 to 3, which comprises using triphenylphosphine, 1,4-bis(diphenylphosphino)butane, 1,2-bis(diphenylphosphino)ethane or 1,3-bis(diphenylphosphino)propane as phosphine.

5. A process as claimed in claim 1 or claim 2, which comprises using bis(triphenylphosphino)palladium(II) dichloride or diacetate as palladium(II) complex.

6. A process as claimed in any of the claims 1 to 5, which comprises carrying out the amidation or alkoxycarbonylation reaction at a temperature of 50 to 60 °C.

7. A process as claimed in any of the claims 1 to 6, which comprises carrying out the saturation of the double bonds in the presence of a palladium or platinum catalyst.

8. A process as claimed in claim 7, which comprises carrying out the hydrogenation in glacial acetic acid or formic acid medium.

9. A process as claimed in any of the claims 1 to 8 for the preparation of compounds of the general formula (I) containing an N,N-diethylcarboxamido, N-tert-butylcarboxamido or N-(2,2-dimethylpropyl)carboxamido group as R^1, which comprises using diethylamine, tertiary butylamine or 2,2-dimethylpropylamine, respectively as an alkylamine.

10. A process as claimed in any of the claims 1 to 8 for the preparation of compounds of the general formula (I) containing a methoxycarbonyl group as R^1, which comprises using methanol as an alcohol.

11. A process for the preparation of a pharmaceutical composition inhibiting the 5α-reductase

enzyme, which comprises mixing as active ingredient one or more 17ß-substituted 4-azaandrostane derivative(s) of the general formula (I), wherein R, R^1 and the ---- bond line are as defined in claim 1 and/or salt(s) of this (these) compound(s) formed with pharmaceutically acceptable base(s), prepared by using the process claimed in any of the claims 1 to 10, with filling, diluting, stabilizing, pH- and osmotic pressure-adjusting and/or formulation-promoting auxiliaries and transforming them to a pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 93/00039

A. CLASSIFICATION OF SUBJECT MATTER

IPC[5]: C 07 J 73/00, A 61 K 31/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[5]: C 07 J 73/00, A 61 K 31/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP, A2, 0 473 225 (MERCK & CO) 04 March 1992 (04.03.92), claims 1-5.	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 1994 (11.02.94)	15 March 1994 (15.03.94)

Name and mailing address of the ISA/ AT	Authorized officer
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/HU 93/00039

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